Diabetes Standards of Care

& Treatment Targets

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Burden of Diabetes

I currently serve as the Chief Scientific and Medical Officer at the American Diabetes Association, but most of my career or prior to the past two years as a staff member has been spent in care delivery in clinical care as well as clinical research, and interestingly last year's speaker for those of you who were here Rich Bergenstal has been a colleague of mine for most of the past 20 years. We have also in Minneapolis, where I have spent most of my clinical time, had a long standing relationship between many of the native communities and the International Diabetes Center working with like Steve Rith-Najarian and others in a program called Stage Diabetes Management that some of you may be familiar with which is really parts and parcel of trying to not just simplify but standardize care for patients with diabetes particularly those that are at highest risk and in particular those that tend to be affected by health disparities.

So what I will try to do today in the next two to two-and-a-half hours is -- got you -- is actually try to talk from the perspective of the American Diabetes Association to give you some understanding of why we as volunteer of health organization and remember ADA doesn't solely health professionals but is part of the diabetes community, in fact, the vast majority of ADA members are people like my mom who are community members either affected by diabetes or themselves living with diabetes.

So I am going to just do a quick poll before I start. How many of you are health-care providers who provide some diabetes care? Okay, how many of you would say, you know at least one individual outside of your clinic who lives with diabetes? Okay, how many of you would say at least ten individuals who live with diabetes?

So that gives you an idea of why maps like this are essentially unnecessary, and I think particularly many of you work where I work in Central Minneapolis the diabetes burden is increasingly significant and I do a fair amount of work internationally just trying to share some of the perspective with the American Diabetes Association. As many of you know there were communities that often when they immigrated to the US were then increasingly affected by diabetes. The good news is we now bring it right to them. So that diabetes is growing in the Middle East, in Eastern South Asia, Africa, and South America.

So what we are facing here in the US is really something that's global in its proportions. These are my disclosures I actually don't do much that interesting and I don't get paid for any of it. As my good friend John Buse said, if actually I ever made investments they always went down so this would be a non-stock tip list, but I will say, my wife works as a Medical Scientist for Genentech and nothing here will touch on that. The other thing I point out that anything I do like this even though I represent the American Diabetes Association they rarely ask me to speak on their behalf and generally deny what I have said.

So it's getting late in the day. These are the three or four major components. I am going to talk about diabetes burden, this is I trust review for all of you. It won't be specific just to the native communities, Alaska natives, but will I am sure touch on what you do and we will talk about it just from the perspective of trends, prevalence and cost.

And then I am going to talk about the standards of care. I think many of you like I struggle with why are these stakes in the ground standards there and where do they come from? Much of that has been the domain of our volunteers at the American Diabetes Association, these are not the American Diabetes Association standards of care, these are the community standards of care that are developed by all of us we hope. And I am happy to entertain questions in that regard, because this is a complex business that we have been in for many years, and there are always controversies around these topics. And then I will talk about what I feel is really one of the greatest opportunities, and I will admit that the Indian Health Service in particular has done some of the best work possible in looking at means of delivering effective diabetes prevention efforts. And then I'll just finish with a couple of comments on what we do day-to-day at the American Diabetes Association, many of you might have met Denise Price-Brown who is here representing many of our high-risk community programs and in particular Awakening the Spirit and others that are available for public consumption.

So what's the public health issue that we're dealing with? I almost find it comical when I'm asked to go up on Capitol Hill and say, this disease that we spend $200 billion a year on, going to approach a-third of a trillion dollars, somehow I have to make the case that this is important, and it effects one in four adults over the age of 60. Imagine like it was said in the previous talk, if cholera affected one in four adults, we'd have no problem getting this on the front pages. But it's a chronic disease, and people live with diabetes, so we still have to do a great amount of work to raise public awareness.

As I said, the numbers, they just keep growing. Generally, 8% to 10% of the entire adult population and this is taking all commerce. It's interesting the new statistics that have been updated with the use of A1C as a screening tool, now suggested close to 80 million Americans are at risk for diabetes or live with prediabetes based on a variety of definitions. The vast majority in fact, it's estimated there are only about 5% to 7% of them who know about it. That means here's a disease that's going to affect one in four that a significant fraction are at risk for, and fewer than 10% of them know it.

It's the seventh leading cause of death, but if we actually did the work well, I mean, how many of you put diabetes on death certificates? It's almost always the proximate cause that ends up on a death certificate - cardiovascular disease, renal failure, complications of peripheral vascular disease and the like. And as we'll talk about it, it is still unfortunately the leading cause of the three major complications of diabetes - loss of limb, end-stage renal disease and loss of vision.

I mean these are numbers I put them in actual numbers because whenever somebody says a 174 billion, it doesn't make quite as much sense to me. That's a lot of zeros and a lot of green, and it's interesting, right now we're lobbying for dollars about $80 million to support the National Diabetes Prevention Program; that's $80 million over several years. And if you even reduce the risk of diabetes by 10% or 20%, you start to save literally tens of billions of dollars. I'm no investor, believe me, but that seems like a reasonable return on our investment.

So this is a gift from my friend, Anne Peters, who works in East LA in the Latino community, and she just took these pictures from her husband a couple of years ago just to underscore what all of you know that one in three children born in the year 2000 is likely to develop diabetes in their lifetime; one in two in the highest risk communities and you see a partial list of

them there. And as I said, this affects one in four adults over the age of 60, and the growth industry unfortunately is affecting the highest risk groups the most actively.

There is some good news in all of this. About ten years ago we thought that the detection of and living with diabetes has shortened your life-span by about 15 years, we've probably reduced that by more than half, although life expectancy is still reduced by six to ten years in the setting of diabetes. So this is not just about complications, this is about quality of life, duration of life and a number of other things.

My friend, Albert Huang, who is a fabulous modeler and mathematician; he can tell me stories that at least I understand, and I'm all about pictures. So hopefully late in the show you are too. This is just the growth, his estimated growth rates in diabetes, and there you've got 40 million Americans; this is adults and children affected by diabetes by the 2030 time interval. His estimates of cost go up, as I said, to about a-third of a trillion dollars, okay, this is direct and indirect healthcare cost; much of it obviously affecting federal programs, Medicaid, Medicare, and all the others. And leaving diabetes unchecked and not addressing diabetes prevention will unfortunately, make this come true.

Several months after Albert published those data, Ed Gregg and colleagues at the Centers for Disease Control actually took the data that they had originally published one in three children born in the year 2000 would have diabetes in their lifetime, and that sounds devastating. But if you think about it, right now its one in four, so that's not a huge step forward. What they suggested is that by the year 2050 one in three Americans will live with diabetes, children/adult doesn't matter. So again the news just keeps getting, I will say more depressing in some respects but I'd say more alarming if you are someone who wants to take action. So ADA and I think all of you are not in the business of just hanging our heads over statistics, but we are actually in the business of trying to do something about this, just watching these lines go up I hope is not what we are here to discuss today.

Standards of Care

So what have we done and how do standards of medical practice help keep our eye on the prize that as I see it is one of the chief responsibilities of organizations like ADA, but like all of your organizations as well. So are these standards of care something we just sat around in a room and got a bunch of middle age males to make up, because that's usually who does these consensus conferences, in fact isn't. Sue Kirkman who is our Senior Vice President for Medical Affairs, he has been at ADA not quite five years, went back and he has found the original position statement on the standards of care, and interestingly this was in 1989, the standards were four pages long, ten references, okay, none of which was original research. So we actually knew very little about the standards of medical care, and this is not that long ago, this is less than 25 years ago. Over the last 20-plus years what ADA has done is collected experts from all over the country all over the world to look at the existing data much of it now based on randomized control clinical trials on everything from diabetes prevention and education, to nutrition interventions, to food sources, to medical therapies.

And I hate to say it, but this is the current summary document. 51 pages of non-stop fun reading this and 395 references, the vast majority of which are actually original randomized control clinical trials or large population observation studies. If you don't have it, it is available

now on iPhone, iPad, Android, downloadable as a PDF, free to any and everyone who wants it.

And interestingly we take as much heat about this as I'd say anything we do, but this is literally used worldwide as a reference standard to say where do we stand with diabetes care? So I will give you the 30-seconds summary of what I think is new, what is most exciting to me is what color the cover is going to be every year, last year it was purple this year it is sort of morose gray, I apologize.

But one thing that many of you are probably aware of is we've gone over the years from the Oral Glucose Tolerance Test almost untenable testing for diabetes. To the use of fasting glucose which had all sorts of controversy, and aren't we going to find too much diabetes really is your concern finding too much diabetes in these days. To now adding the A1C, this integrated measure of glycemic burden. And interestingly the WHO took two more years than we did to adopt this much of it required standardizing the test, but now right after the oral contraceptive or IUD party you should get an A1C on folks when they show up because particularly in high-risk communities this is a simple screening test where the pretest probability is so high that not doing the test rarely make sense.

And we have also expanded as you can see the at risk categories using A1C, that's a bit more controversial, are we going to put a bunch of time and effort into preventing diabetes in people who many never develop it? Yes, we may, but when was modest calorie restriction and increased physical activity a bad thing to recommend whether your diabetes risk is high or not.

And then things like self-management. This is not just about medical therapy the ADA along with partners at AADE wrote the book and in fact set the standards for diabetes self-management education. We got Medicare to adopt our accreditation and recognition programs so that this can be reimbursed in a medical setting. I have spent my years with a huge number of incredibly talented diabetes educators. To me this is one of the cornerstones of diabetes management.

And then Complications Management, if diabetes was simply symptomatic hyperglycemia we probably have a relatively easy job, but most of the treatment targets glucose, lipid, blood pressure and otherwise are designed to focus on complications.

And then don't forget that these are people with diabetes, this is not the diabetic, and if I can get on my soap box there are no diabetics, diabetic is an adjective not a noun, remember these are people who live with diabetes just like they live with cancer, hypertension, heart disease and the like, and I will spend my remaining days emphasizing that to people.

Treatment Targets

Glycemic Control

So let's talk about the standards of care. What have we learned and how many of you have heard of something called the ACCORD Trial? Okay about half the hands. I am glad the other half didn't because it's caused more trouble than it's probably solved, and I was on the steering committee so I can poke a lot of fun at the ACCORD Trial. But I will talk about it in this setting

because there was a lot of the sky is falling and we should be really careful what we do in diabetes. I am here to give you I think a slightly different perspective.

So if you're like me and you pay attention to about one out of every 11 slides, this is the one actually to pay attention to. These are the standards of medical care for diabetes for the most part when it relates to treatment targets. A1Cs is below 7% with self-monitored blood glucose values in the ranges noted, blood pressure is under 130, LDL is under 100. Now remember, every one of these is a cut-point. It is a dichotomous cut-point in something that is a continuous metabolic variable or cardiovascular risk factor, and inherently there is error anytime you put a single cut-point on any continuous medical or biologic variable. What I see these as are marks in the sand. These are like for me par in golf. This is not the thing that everyone must achieve to be well-served but it should be sort of that beacon of light that keeps us focused on glycemic control, blood pressure control and the management of dyslipidemia. I rarely break par in golf, I suspect that's true of many of you. But the USGA isn't going to change par just because I am a bad golfer. Nor should we probably change these standards because sometimes it's challenging to achieve them.

So let's start with A1C, because this is one that in particular has received a lot of attention of late, and I am a college History Major. How many of you had undergraduate majors that have absolutely nothing to do with what you do for a living? Okay, good for you. But you have that point in time my daughter who is graduating with her Geography degree, sat up four weeks ago and said "what in the world do you do with a Geography degree?" So she is going to teach Math of course.

I went into Medicine, you all did the same, but I actually find the history of what we've come to understand for the standards of care, very important to understand. It actually started in the 1960s with something called the University Group Diabetes Project (UGDP), and I am just going to let it grow to show you that these standards didn't just come from either my whim or an absence of clinical data. This is three or four decades mostly of randomized control clinical trials looking at more versus less intensive glucose control as it relates to complications, everything from microvascular complications to macrovascular complications which have been studied more recently. And I guarantee you this isn't only a partial list, this is I would argue anywhere from 50,000-200,000 patient years of information.

So remember, we don't change our standards based on the most recent test, there is something called the Recency Effect. You'll only remember what you heard last. Don't forget all the things that have happened over the last 40 years. I mean the standards of care kind of fell right in the middle of this and have evolved we hope with the data.

As I said I am a picture guy, so if you like simple summaries, this might be one of the other four-five slides to pay attention to. We have known for years that the higher your estimated average glucose, your ambient glucose, or your A1C, the higher your risk of retinopathy, nephropathy, and peripheral neuropathic disease; it's this curvilinear relationship. What the vast majority of all these trials have shown, and in fact I will show you a summary table later is that in fact the opposite relationship also holds. Any lowering the blood glucose over time reduces the inherent risk of microvascular complications in diabetes.

Now what you can see from the way I have drawn this is actually the greatest benefit occurs when you lower blood glucose from very, very high levels to even moderately well- controlled

levels, but the benefit continues two levels at or near normal. Now, why choose a target of 7%? Again as I said, you are sort of picking a dichotomous cut-point that just falls somewhere along this line. But, as you can see, the absolute return starts to diminish as you get below 8 to 7.5-7% A1C. But if you're talking about an individual who wants to maximize their chance of reducing risk, it makes sense that the standard of care is optimized, that is, it's an optimal target. Not that everyone should have the same target but it keeps that beacon of light in front of us.

So this is roughly the same set of studies that I showed you in a moment, but it actually looks at it slightly differently. This is laid out not by when it was done in time, but actually when it was done in time for each of the patient groups that was randomized, those with relatively recent onset diabetes, Type 1 or Type 2, and those with longer duration diabetes, because one of the questions has been and I am sure this affects your clinical practice and thought is, when is it too late? If I waited ten years, it is ten years of glycemic burden, a time where I should toss in the towel and focus on other things? And I will hopefully show you data that says it's never too late.

But let's start with some that were done early in the course of diabetes. In the UK, Japan, and in the US, Type 1 and Type 2 diabetes, pretty clearly whether you talk about eye disease, nerve disease, kidney disease, every time you lower A1C from higher levels to lower levels, you see a reduction in microvascular disease risk. I honestly dare you to show me a study where either the opposite has happened or at least some trend towards a reduction in risk hasn't been demonstrated. What I have shown at the top in simple terms is the mean A1C in the standard treatment group and those that were treated more intensively.

In the large US Type 1 diabetes trial from 9 to about 7, in a larger Japanese and British study you can see they went from similar levels although slightly lower in the UK study down to about 7%. And for every 1% reduction in A1C there was about a 20 or 25% relative risk reduction in the rates of retinopathy, neuropathy and nephropathy. So this is reasonable evidence to me that suggests that at least having a concept in mind of getting at or near this 7% target makes some sense relative to microvascular risk, and I am actually showing you real data here, these aren't my made up pictures, from DCCT and the UK study. And while I can draw the box around that area, to me intellectually it looks like we are starting to optimize the benefit at or about 7%. Now does that mean this comes without a price? No, this is more effort particularly on behalf of the patient, it is often more therapy, it is often more complex and often comes with a risk of weight gain and hypoglycemia. So everything in life is a balance between these benefits and risks, but again don't take your eye off that prize.

The other very interesting thing that I think and I've followed some of these DCCT patients in my own clinic for more than half their life, many have been involved for more than 20 years is that early intervention carries later reward, even if control isn't maintained at the same intensive levels in the DCCT. As you can see here, the orange line shows people who had six or seven years of very good "intensive" control and then after the DCCT both groups became about the same but they're in this case was what we called Metabolic Memory. Some early improvements in control and control benefits many years later and interestingly in the UK study where they followed them for another ten years after the cessation of the more intensive therapy, the same was shown. They call this the Legacy Effect, so whether you call it Metabolic Memory or the Legacy Effect, any early intervention carries benefits 5, 10, 20 years later. And when I talk to patients in clinic when I am trying to encourage them to get good

control as early as possible, in a sense this is like saving for retirement. While it's tough to get a 20-year-old to save for retirement, it is so much greater in terms of benefit when you start early, and diabetes management particularly glucose control carries some of those same benefits. Of course my daughter wants to spend money today, she is not thinking about retirement. So part of our job is to give people the tools they need to at least start to think about saving for retirement.

This is the ACCORD Trial and while ACCORD - as some of you who raise your hand know was designed to answer a question about the intensity of glucose control and the impact on cardiovascular disease - it actually embedded within it a second question which was around a single microvascular complication. We almost always measure eye disease in clinical studies because it is eminently the most measurable, probably the best standardized in terms of measurement, and if something is going to be impacted in the near term we think it is retinopathy.

The ACCORD Eye Study was published by Emily Chew and colleagues from the National Eye Institute about a year ago. And suffice it to say this is a study that wasn't looking at standard control from the 1960s which was an A1C of 9%, it was talking about the new standard control which is A1Cs at or about 7-7.5% versus what I will argue was ridiculously intensive glycemic control trying to normalize A1Cs less than 6% in about 5,200 people. And that took an incredible amount of effort, ultimately, did not reduce the risk of cardiovascular disease as we will talk about. But the question is, is going to 7-7.5% good, how much additional benefit do you see in terms of eye disease going from 7.5% down to near 6%? The answer just so you don't have to read this chart in detail is there was about another 30-35% reduction in the risk of eye disease. Now this also wasn't just a few dots and spots in the back of the eye. This was photocoagulation, laser therapy. Change in vision, a three-step change on the vision chart. These are really to me the hard endpoints of retinopathy that obviously precede vision loss completely. It suggests that going even lower carries some additional benefit. Now does that mean the A1C target should be less than 6% for all patients with Type 2 diabetes based on this? Clearly not, but it further underscores what I've said earlier that the lower the better in terms of microvascular disease risk.

Interestingly, the fibrate drug, Fenofibrate, this is the second study where unexpectedly it lowered the risk of retinal disease. Probably does not in general apply to heart disease. So a drug that we've been giving to people for lipid disorders and heart disease which seems to have a neutral effect if you give it to everyone, two times in a row has actually reduced the risk of retinopathy. So bit of a surprising result and more research to be done.

So I hope I've convinced you that glucose control is a reasonable thing. Remember that diabetes remains the leading cause of complete vision loss, the leading cause of lower limb amputations. The relative risk of limb loss in diabetes is anywhere from 7 to 11 fold higher. That's 700-1100% higher. Amputations occur essentially in no other circumstance save trauma. And it is still the leading cause of end-stage renal disease particularly in some of the highest risk communities. So intensive glucose control, I would argue initiated as early as possible is what's of benefit in both Type 1 and Type 2 diabetes.

So what about the issue of the other major complication of diabetes and that's cardiovascular disease? I've highlighted three studies; one is called the VA Diabetes Trial, the Advanced Trial, which was a global study of more intensive therapy, and then the ACCORD Trial, which I've

described. This relationship which is just a recapitulation of what I showed you earlier suggests that lower must be better. This is what happens for my microvascular diseases, but interestingly while diabetes is clearly a risk factor for heart disease, the relationship between glucose alone and heart disease risk actually looks slightly different, and that's what these studies were looking to address.

So the rate of heart disease goes up as your glucose up, but in a much slower and probably a more linear rate. So that's what suggests that if glucose control alone aside from blood pressure, lipids, not smoking, using antiplatelet therapy has a benefit, it is likely to have a benefit that follows this slope. You have to be careful. Epidemiology can mislead you but I have said to people, my good epidemiology friends, epidemiology rarely lies. It just generally exaggerates. So the question is, how much is glucose lowering going to do for us in terms of reducing cardiovascular risk?

Now I've hopefully saved all of you hours of reading. Some of the primary articles here are well-worth reading. One of the reasons I'm convinced I became Chief Medical Officer of the ADA is not because of what I know, but I actually know a lot of really smart people who give talks like this and I just copy from them.

Just look at this chart. These are big studies done that at some point could assess whether glucose lowering reduce the risk of microvascular disease, heart disease, mortality or all three? In general all of them in the more intensively treated groups got to A1C values at least on average of at or about, and in some cases below 7%. The number ADA has been holding forth as "the standard of care or the treatment target."

Every one of these trials, short-term and long-term, when you look at those microvascular complications that we were powered to assess, meaning, we had the statistical power to assess them, the arrow went down. Now you can argue with me and Rich Bergenstal and I put this chart together for a paper we published this last year. The magnitude of the effect and the absolute benefit, depending on where you started, differed but the arrow never went any direction but down. For heart disease and mortality you can see quite a different story. There are no short-term clinical studies that have actually confirmed that glucose lowering per se, whether it's going from very high to moderate, or what we would call now, standard, or from standard to ridiculously intensive demonstrated a short-term reduction in cardiovascular risk. Only two long-term follow-up studies, the UK study and the Type 1 DCCT, suggested that good control here paid benefits for your heart here 7, 10, 15, even 20 years later.

So if you want a summary why at least I feel the data support the current A1C target, all you have to do is look at this first box. This is why intensive glycemic control was first considered important and tested. You reduce the risk of microvascular complications, you may, I emphasize, may have some later benefit on cardiovascular disease. But lipid control, the management of hypertension, and other interventions probably supersede glycemic control in terms of their importance to control cardiovascular risk. And the reason ACCORD became a bit controversial is it was interrupted early when we were trying to get these very, very low glucose levels. They were actually more deaths, fewer heart attacks, but more deaths in the intensively treated group. So this is where I see a lot of people through the proverbial glycemic control targets out with the bathwater saying "My goodness, we don't prevent heart disease and we kill people. We should stop immediately". And I very quickly step back. And say, I agree that not every patient with Type 2 diabetes who is 65-years-old in the setting of multiple

chronic diseases should have an A1C less than 6%. But the first column here says the glycemic control for reducing the burden of microvascular complications remains important.

So what did people say? They said, oh, it must be that we shouldn't intensify therapy in older individuals with heart disease, who are using insulin who have long-standing diabetes. But in fact when we looked at the ACCORD data, it turned out that older individuals did no worse than younger individuals when the control was safely intensified. That, in fact, if they were able to successfully get their A1C under 6% their mortality was lower. The mortality risk was actually in those individuals who we continually attempted to intensify control and were unsuccessful. So as I say to people, they declared themselves as complex, complicated patients who maybe at higher risk. This didn't surprise us in the end.

Insulin therapy was not associated with higher mortality risk. It was associated with a higher risk of hypoglycemia. It maybe that after you've had diabetes for 20 or 25 years that at more intensive control, and I mean very intensive control, should probably be carefully considered. It turned out that those people who've lived with very high glucoses for many years, who'd probably been unsuccessful at achieving more intensive control, again declared themselves before we even started the study if they came to the study or develop significant hypoglycemia during the course of the study that was probably another bellwether to step back. That's not rocket science. It makes some clinical sense. As I said, those who didn't respond to our efforts to improve control.

So what do we do with glycemic targets in adults? Do we suddenly change them to 8 or 9% and go back to the 1950s and 1960s? Absolutely not. I hesitate, and in fact, the American Diabetes Association takes a lot of grief for having its target as less than 7%. The WHO, the idea of the European Association for the Study of Diabetes, every other international organization actually has its target that is 6.5%. We are on the high side yet we are taking a lot of grief. ACC, the American Heart Association and everyone else has stood in line to say based on the data we should stay there. Because lowering of A1C reduces microvascular risk, probably doesn't help your heart in the short-term, but does not collectively increase the risk of mortality. When you take all of this information together and the sooner you do it and more safely you achieve it, probably the more likely you are to have a long-term benefit even for cardiovascular disease. As I said there maybe even some small incremental benefit to going even lower. It depends on who you are, what you do and how you try to achieve it.

So that makes individualization critical. This is actually from a paper a couple of weeks ago. When we talk about individualizing care, so when you're sitting in the room with a patient and you say, you know what, I don't know if this is somebody who should be targeting less than 7% or very aggressive blood pressure control. This is a chart that my friend Silvio and Zucchi (ph) and some colleagues took and I've adopted it. How do I know whether I should go to the more intensive or the less intensive side for an individual patient? Well some of these are actually critical factors that you and I only know when we talk to people; they are behavioral, they are social, they are economic. If this is burdensome in any of those areas, then higher targets are likely reasonable. They shouldn't be the default, but they could be considered reasonable if those things become restrictive.

As I said the risk of hypoglycemia, if you're 85 and you lived with diabetes for 20-plus years, it's unlikely to getting an A1C of 6% is going to provide substantial benefit. Disease duration, when it gets beyond 20 or 25 years, and obviously the more established co-morbidities that

aren't reversible, end-stage renal disease, complete vision loss, shorter life expectancy play into this decision. But you can see that doesn't preclude going to lower targets in people who do not have these characteristics. And finally, the establishment of complications. It's not too late. In fact, one of the first studies done in Type 1 diabetes took individuals with almost 20 years of Type 1 diabetes, and still reverse the rates of progression of renal disease and eye disease. So I always tell patients that the time to start is now, but it's never too late that we can intensify therapy at some point.

So what do you make of all that, what do I make of all that? I added this because everybody was putting in really clever quotes, and I have to go back and get one of my favorite. "Everything should be made as simple as possible, but no simpler", and that was Einstein as well.

So what's my glycemic target for an individual patient with diabetes? I presented this couple of years ago at the ADA meetings. I said, it should be as low as possible, as early as possible, for as longer period of time as possible, as safely and as rationally as possible. This is not a number; this is an approach to an individual. So for what that's worth, I think it allows us to individualize care, whether it would be diabetes or anything else. So I hope that's as simple as Einstein would like it, but no simpler, and I hope the data support that.

Blood Pressure and Lipid Control

So I'm going to finish with two other discussions; the first is of lipids and blood pressure, and I'll go through this quickly because we're running short on time. But glucose control isn't the only thing we need to think about in diabetes and I'm certain that all of you think about blood pressure and lipids. This is where I'm going to go back to the ACCORD experience and try to demystify some of what we learned.

Here is the epidemiologic relationship between blood pressure and both heart disease and microvascular complication. More like glucose, it's linear. It looks like lower is better, but the question is how low should we go when we're aggressively initiating therapy.

The UK study from which this picture was originally described actually took blood pressure from 155 to 145, showed a great benefit. So does that mean the target should be 145? Another large study, the ADVANCE Trial took them from 140 to 135, still got some benefit, particularly for renal disease as you might expect. The ACCORD Trial said, just like it did for glucose, what about really ridiculous blood pressure control? Take people with longstanding hypertension, which many of you know is very difficult to treat, and lower them down to less than 120.

Now I will tell you when I started the ACCORD Trial I thought glucose control would be the most challenging. Blood pressure control in a population with longstanding hypertension where you are trying to get to 119 or below is very challenging. I mean, I remember looking at patients and trying not to giggle or cry when their blood pressure was 122, saying, sorry, not good enough. Here's your Reserpine. And I did use Reserpine, it turns out it works.

So this one you don't want to forget. This is the study designed for ACCORD, immediately put this out of your mind. Basically, there were two other sub-studies; good versus very good blood pressure control, and statin versus statin plus a fibrate, whether we should add a fibrate to

everyone, that's where we found those eye findings I described earlier. Basically we said, you know the target is less than 130 because that seems to protect from kidney disease, maybe from eye disease, maybe less heart disease in those with diabetes. But we said, shouldn't we go even lower based on what epidemiology taught us? This took three, four, five drug anti-hypertensive therapy, aggressive timelines and milepost, where if your number was too high we added something. This was done in an attempt to overcome all the clinical inertia that all of us face, and it was target-driven. It didn't matter how -- I did it with leeches, I did it with bleeding, I did it with anything, tilt table if I have to. So again, I wouldn't say clinically practical but really trying to assess whether the target was appropriate.

And honestly we did it. I was stunned by this. You can see on the red or orange line we got their blood pressure down within a few months and kept it under 120 for the duration of this study. Now fabulous, you would think this has got to have some benefit.

There is the Kaplan-Meier curve, and simplifying - that basically there was no additional benefit in a population with established heart disease or significant heart disease risk that going from a target of less than 140 to a target of less than 120. Now the caveat is those in the standard group, I actually got some of the best blood pressure control I've seen in a clinical trial, about 132 or 133. It's actually closer to the current target than 140, which was the established target for the study. So more intensive control is probably not necessary for the vast majority of patients with Type 2 diabetes, but as we know about hypertension the one thing that went down was stroke. It's the least common cardiovascular event, MI obviously being the most common, but for those of you have taken care of anyone post-stroke it is clearly one of the most devastating complications of heart disease and in particular hypertension. It was a 40% reduction in fatal and nonfatal stroke. So this should again be a sign that there are some people for whom more intensive blood pressure control still may work, and there is this again, okay.

What about this lipid piece? This was the only blinded part of the study, but I think actually taught us a lot. Many of you likely as I do see diabetes patients who are on a statin, their LDL is 85, their HDL is 22, their triglycerides are 200, and you wonder what in the world do you need to do. Do you add a Fibrate, Niacin, aggressively treat all of those people? So this was actually designed to answer that question, everyone got a statin. If they couldn't take it we used other ways to lower their LDL and give them alternative statin therapy. So we want that out of the picture as a variable and then added either a fenofibrate or placebo. And as you can see the vast majority were on and stayed on a statin, and this had no added benefit except for eye disease which I showed you earlier.

There was no further reduction in cardiovascular risk with the exception of those individuals perhaps with the very, very low levels of HDL and high triglycerides. But what this suggests is that at least blindly we should not add a fibrate to every Type 2 diabetes patient we see, but statin therapy and LDL targeted therapy as has been recommended for a decade or more is rational.

So suffice it to say that the NIH and other organizations put about a half a billion dollars into this, and it turns out as I suggest that our targets were pretty good all along. Now are they perfect, and does this raise additional question? Certainly they're not perfect and there are other questions but I'm reminded that all of these complex things when we try to simplify them actually come back to clinical common sense. The data have to be there to support us.

And so another one of my favorite quotes is this one. “So after observation and analysis, when you find that anything agrees with reason and is conducive to the good and benefit of one and all, then accept it and live up to it.” This is nothing recent. This is from –Buddha. So 1500 years ago we had our clinically practical guidelines for care from the Buddha. Don't forget these things.

Diabetes Prevention

Let me finish with a quick discussion of diabetes prevention. We have talked about this earlier when we talked about Screening and Prevention, using A1C, using fasting glucose is an enormously valuable tool, particularly in high-risk populations.

And the reasons to screen are probably manifold but twofold in particular, particularly for the communities that you serve. One is the prior probability of the test being positive is so high - we do colonoscopies in hundreds of thousands of people where the pretest probability of colon cancer is clearly less than out of 1 in 25% - that's five people out of a 100 who have the disease. Here we're talking about with pre-diabetes and diabetes, a good one in three chance that you are going to find something, and we usually don't diagnose diabetes, we discover it. It's been around for three, five, even ten years when we detect it. And these are data from Maureen Harris. She has done this in native community, she has done in the African-American community, she has now done it overseas. The rates of complications of diabetes are often 10%, 20%, 30%, even 50% when the disease is discovered. So getting there early as I said makes a difference, and that's where screening and detection make a huge difference.

So who do you test and how? Believe it or not we get a lot of grief for this that saying, testing should be considered in anyone who is overweight who have additional risk factors. Those risk factors you know well, anyone with a first degree relative with diabetes, any higher risk population group in this list is growing all the time. Any other chronic health conditions, heart disease should be a marker for diabetes and vice versa. Any prior history of a glucose value that’s abnormal, any history of gestational diabetes or a child that’s born with a bodyweight of nine pounds or greater. And then some other less common conditions, but morbid obesity becoming increasingly common, things like Acanthosis, the polycystic ovary syndrome and the like.

So if you have even moderate overweight and in some populations BMI is much less than 25 in any of these conditions, screening at or above the age of 40 or 45 is appropriate. And if normal, you should repeat it every three years or so, because again the population risk is so high. For any community at even higher risk, testing should begin earlier and should be done more often. Now, are those very general recommendations? Yes, because how early is too early. As a Mdewakantonwan Sioux girl that I have taken care of in Minneapolis, who was four, who developed Type 2 diabetes just after her third birthday. I'm not screening 3 and 4-year-olds, but you know your community very well and should consider earlier screening as is appropriate for that population.

So what is screening? So I think, people are misled that screening is a blood test. Screening is understanding your risk. The CDC has tools on alert day, which was just a few weeks ago, the American Diabetes Association had 600,000 or 700,000 people. Just go online, take this

simple test and find out if they were green, red or yellow. So screening is being aware and then coming to you as a provider to get a detection test, that's very different than screening. Just going out to your local mall with a blood glucose meter is not screening, in fact, we don't recommend it, because usually who use screen are people who already know they have diabetes or people who are as my wife says, 16-year-old vegan marathoners who probably aren't at risk.

So use these risk tests, they are the same for CDC, NIDDK and ADA. One group doesn't buy this. It's unfortunately the U.S. Preventive Services Task Force, who I have got more bones to pick with and maybe even you, but suffice it to say that we think screening and detection is important. And this is just one example of where your risk might fall. When you fill in the answers, if you are green, you are good, if you're yellow or red, you should see your health-care team.

So why find diabetes or even prediabetes? Again years, probably decades of clinical studies, these are studies in China, in Finland, in the US and in India that looked specifically at whether moderate weight loss and physical activity reduce your risk of diabetes. If you're at high risk, everyone of them cut the risk in half. Is that delay or is it prevention? Turns out it's actually both, both of which have a benefit, they have a financial benefit; they have a disease-burden benefit.

So if you remember nothing else from diabetes prevention, screening and detection and simple, hopefully community-based measures at helping people, set up a plan to lose modest amounts of weight, 5-10% of their bodyweight and remain physically active or increase physical activity to 100-150 minutes a week.
Here's the US Diabetes Prevention Program more than a 50% reduction. Now did we cure everybody? No. You still have to be aware that people at high risk will go on to develop diabetes, but isn't it nice to know that the same intervention weight loss, physical activity, diabetes self-management, education, and in some cases simple therapies like Metformin then can be added. So you get to people earlier and the easiest people are to control are those you find the earliest.

What do lifestyle interventions do? Well, obviously you target it at those at highest risk who then have an elevated fasting glucose or A1C, the therapy that works the best carry things like balanced low-calorie nutrition; I heard Darryl Tonemah and Wes Studi talk a few weeks ago about heritage foods. Those are balanced low-calorie, whole-grain, high-fiber nutritious approaches. These are not novel, power-bar like approaches to nutrition. Regular physical activity is what you did this morning. Just walk and just start walking as soon as you can. If walking is impossible, look for alternatives like swimming, water aerobics. And then maybe the most important is not high technology, it is frequent intervention and support, which is nothing more than encouragement and almost all of the ones that work are based in a community. They can be clinically supported, but they are community-based.

I'll show you at least one example. This is the US YMCA. It turns out that like 90% of US adults live within three or six miles of a YMCA. Not all of us do, and I couldn't find mine for the world. But if you're taking a hundred individuals that you screen and detect as being at high risk, you use the Diabetes Prevention Program-like intervention. Teach them with anybody you can find who is a good teacher. They don't have to be a healthcare provider. You prevent 15 cases of

Type 2 diabetes in hundred individuals over three years. That's an enormous return on a relatively low investment.

You prevent a lot of missed work. You prevent the need for not diabetes therapy, but blood pressure and lipid management in 11 of the 100. You prevent $100,000 in healthcare cost, and this program costs about $200 a year. So that's a $600 investment per individual and you add the equivalent -- any of you know who about QALYs or Quality Adjusted Life Years? Does anybody actually know what that is? I have no idea. I love the way Ron Ackerman talked about this. You basically add 20 years of perfect health to these 100 individuals. Now I don't know who and I don't know when, but that's a great way for me to think about the benefit of this intervention.

So did it work? It worked in the first six months, the next 12, 20, and 28 months. Now this is weight-loss which they're using as the early surrogate for prevention in this YMCA program, but it clearly worked and was cheap, effective and community-based.

Now if that doesn't work, are their medicines? Yes, but medicines it turns out are clearly second-line therapy for diabetes prevention. The best of them is fortunately the first thing we generally use in diabetes which is Metformin.

So if they develop diabetes or they fail to respond to your lifestyle intervention, you've already got your answer and it's what you do if they developed diabetes. It turns out in the Diabetes Prevention Program, Metformin fell between doing nothing and lifestyle intervention. So whenever you think medicine is the easy way out, it turns out in this case it is not.

So I am going to finish with just a couple of comments and that's the balance that I see between the public health approach to diabetes and diabetes prevention, which is what I've just talked about, which is all of these things. It is weight management, food policy, food behaviors, nutrition support, increased activity, prevention efforts, which aren't medications necessarily and then just understanding risk. These are low-cost, sometimes high intensity interventions that require a very integrated service on your part, but they are eminently doable. If the YMCA can do this, we can all do it. That's different than clinical care. Once you have established conditions like hypertension, hyperlipidemia, diabetes, now we have to add in the components of clinical care delivery, medical management, drug and device hospital care, long-term support. But really this is the continuum as I see it between diabetes prevention and diabetes management. And I've hopefully provided you some insight why I think the standards of care are important, and why in fact, both prevention and management can pay huge dividends.

So I'm going to just finish by showing one other set of components that I think are important. What I've hopefully reviewed is that diabetes awareness screening and detection are critical. That treatment and complications prevention are based on the standards of medical care, that is, the standards are designed to reduce the burden of disease. And understanding and addressing how this is best delivered in your community is probably more important than remembering any one number I told you about today, and then what more can or should you do.

The American Diabetes Association now more than a year ago started the Stop Diabetes Movement, which is not just about preventing diabetes, but stopping its effect on

complications, preventing discrimination against those with diabetes, those looking for employment with diabetes. Anything you can do to support this in your community or with us at the ADA is much appreciated.

Again, Denise was showing some highlights from our Awakening the Spirit, the ADA, I will tell you, because I was up on the hill assuring that special diabetes funding was continued the $600 million over the next two years; absolutely essential. I can raise a hundred bucks for my mom if I shake her down hard, but to get 600 million bucks from the feds is absolutely invaluable.

A couple of programs that are just clinician support tools, the estimated average glucose, which is how do we help patients understand what an A1C means in terms of their glucose result available free online, the ADA professional website and our website. And then a brand-new program called ‘Living with Type 2’ our patient initiative is also a part of the support we can provide you in the primary care community.

I love this quote. “The intuitive mind is a sacred gift and the rational mind a faithful servant. We have created a society that honors the servant and has forgotten the gift if we don't be careful”.

Thanks very much!